# Natural Killer Cells: Their Role in Defenses Against Disease

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*Summary.* Natural killer cells are a recently discovered subpopulation of lymphoid cells that are present in most normal individuals of a range of mammalian and avian species. Natural killer cells have spontaneous cytolytic activity against a variety of tumor cells and some normal cells, and their reactivity can be rapidly augmented by interferon. They have characteristics distinct from other types of lymphoid cells and are closely associated with large granular lymphocytes, which comprise about 5 percent of blood or splenic leukocytes. There is increasing evidence that natural killer cells, with the ability to mediate natural resistance against tumors in vivo, certain virus and other microbial diseases, and bone marrow transplants, may play an important role in immune surveillance.

Natural killer (NK) cells were discovered, only about 7 years ago, during studies of natural cell-mediated cytotoxicity. Attempts were being made to understand a puzzling series of observations in tumor bearers or in individuals immunized against tumors. Investigators expected to find specific cytotoxic activity against autologous tumor cells or against tumors of the same histologic or etiologic type, and indeed they did find such activity in some studies with virus-induced tumors in rodents (*1*) and with some cancer patients (*2*). However, lymphoid cells of entirely normal individuals also reacted against some tumor cells or cell lines derived from tumors (*3*). Much of the natural reactivity was found to be attributable to a particular subpopulation of lymphoid cells, now termed NK cells. Studies on NK cells have recently expanded into a broad and multifaceted area of research (*4*), stimulated by the increasing indications that these cells may play important roles in natural host resistance against cancer and infectious diseases.

Before considering the evidence for a possible role of NK cells in resistance against disease, we summarize the characteristics of other, better known categories of immunologic effector cells and discuss their similarities with and differences from NK cells. Some of the general and functional characteristics of each cell type are given in Tables 1 and 2.

## Characteristics of T Cells

The two main categories of lymphoid cells that can recognize and react against a wide range of specific antigens are T cells and B cells. B cells are responsible for antibody production and their characteristics and functions have been extensively defined (*5*). However, B cells do not appear to function as direct effector cells for reactivity against tumors or microbial agents and will therefore not be discussed here. T cells are a major subpopulation of small, typical lymphocytes that are dependent on the thymus for their maturation and acquisition of functional activity. Their phenotype has been studied extensively and several selective markers have been found on virtually all T cells.

In man, receptors for binding to sheep erythrocytes, and in mice, the Thy 1 or theta antigen, have been the most widely used selective markers for T cells. Recently, a series of monoclonal antibodies to lymphoid cell populations has been developed, and antibodies 9.6 (*6*) and OKT3 (*7*) have been shown to react with almost all human T cells but not other cell types. Similarly, in mice, monoclonal antibodies to Thy 1 and Lyt1 (*8*) have been shown to react selectively with most T cells. In addition, some antibodies have been associated with functional subpopulations of T cells. Of particular note, Lyt2 and Lyt3 in mice (*9*) and OKT5 or OKT8 in man (*10*) have been associated with cytotoxic T lymphocytes (CTL) and suppressor T cells. T cells actually seem to be a very heterogeneous collection of cells with a wide variety of clones, each restricted in its reactivity to a particular antigen or a set of cross-reactive antigens. For optimal or even adequate recognition of most antigens there appears to be a requirement for the T cells to interact not only with specific antigenic determinants on cells but also with products of the major histocompatibility complex (*11*). The chemical nature of the antigen recognition structures is not completely defined, but a component appears to be the variable portion of the heavy chain of immunoglobulins ($V_H$ region) (*12*).

T cells have virtually no detectable spontaneous cytotoxic or other forms of activity, but rather must be activated, usually by being exposed to specific antigens on accessory cells such as macrophages (*13*). Thus there is a considerable latent period, usually 7 to 10 days or more, before T cells develop their initial or primary reactivity. Then their reactivity often subsides to low or undetectable levels. Upon reexposure to the antigen, a characteristic feature of T cells is to show an accelerated memory response, with development of high levels of activity within 2 to 5 days. For most T cells, such antigen recognition is the sole basis for interaction with target cells. There have been some reports of antibody-dependent cell-mediated cytotoxicity by typical T cells, via their receptors for the Fc portion of immunoglobulin M (IgM) (*14*). Also, the receptors for the Fc portion of IgG on a small subpopulation of T cells may be important for some of their reactions. However, most such $T_G$ cells are probably NK cells and the more well-known K cells that mediate antibody-dependent cytotoxicity.

Although the main physiological signal for activation of T cells is the specific antigen, a variety of other factors nonspecifically activate T cells or increase their reactivity. Some plant lectins (for example, phytohemagglutinin and concanavalin A) can induce polyclonal activation of T cells (*15*). Most of the other factors listed in Table 2 appear to be unable by themselves to induce the function of T cells but rather act in an accessory or facilitatory way, after triggering the immune system with antigen. One of these activating factors, T cell growth factor (TCGF or interleukin 2), promotes

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the proliferation of T cells (*16*). This appears to be an important amplification system for T cells and, by using TCGF, an overall population of T cells or specific clones of T cells can be expanded and grown in vitro. The activity of T cells also seems to be well regulated in a negative direction by a variety of cells and factors (*17*). In addition to antigen-specific suppression of T cell function, there are various nonspecific inhibitors of their reactivity. Some factors can regulate activity in either direction; for example, interferon, when given before antigenic challenge, can enhance delayed hypersensitivity reactions and, when given with the challenge antigen, can inhibit reactivity (*18*).

One of the main functions of T cells is to be able to directly interact with, and cause the lysis of, target cells bearing antigens to which the T cells have been previously sensitized. The actual mechanism for the lytic activity is unknown. However, a series of complex steps have been defined (*19, 20*): (i) binding of T cells to targets by way of the surface receptors for target cell antigens, (ii) programming for lysis, and (iii) the actual lytic event. The CTL can recycle and go on to kill other target cells via the same steps. Two main possibilities have been suggested as the mechanisms for the lytic event: (i) serine proteases, since cytotoxicity has been inhibited by inhibitors of these enzymes (*21*), and (ii) osmotic alterations in the target cells, leading to swelling and disruption (*19*).

Some T cells, probably different subsets from CTL, can also mediate indirectly a variety of effects on target cells and on other lymphoid cells, by their production of a wide variety of lymphokines (*22*).

### Macrophages, Monocytes, and Polymorphonuclear Leukocytes

Macrophages, monocytes, and polymorphonuclear leukocytes (PMN's) are the other main categories of well-known effector cells. These cells share many characteristics but in most regards they are quite divergent from T cells. Macrophages and monocytes represent different stages of differentiation of the same cell type, and they and PMN's are derived from common myelomonocytic bone marrow stem cells. They are all large cells with abundant cytoplasm, containing a variety of histochemically identifiable enzymes, and have the particularly characteristic properties of adherence to plastic and other surfaces and of phagocytosis of a variety of particles, including microbial agents. Most or all of these cells also share some cell surface markers: for example, receptors for the Fc portion of IgG, the ganglioside asialo GM1, and the human cells react with the monoclonal antibody OKM1 (*23*). In contrast to T cells, both macrophages and PMN's have natural, spontaneous cytotoxic (cytolytic, cytostatic, or both) reactivity against tumor cell lines (*24, 25*). In addition, they are rapidly activatable, within hours to 1 day, to considerably higher levels of cytotoxic activity (*26*). Most of the activating factors are nonspecific and include lymphokines [for example, macrophage activating factor and interferon for macrophages (*27*)], phorbol esters for both cell types (*28*), and microbial products, particularly bacterial endotoxin for mouse macrophages (*29*).

Normal macrophages or PMN's can also interact with, and have considerable cytotoxic effects against, IgG-antibody coated tumor cells (*30*). Similarly, antibody-coated bacteria or other particles are efficiently phagocytosed by these cells. A major aspect of the cytotoxic activity of both cell types relates to the myeloperoxidase-dependent generation of reactive oxygen species (*26, 31*). However, this mechanism does not appear to be solely responsible for their microbicidal and antitumor cytotoxic effects, since the cells from myeloperoxidase-deficient patients with chronic granulomatous disease still have some cytotoxic activity (*31*). Stimulation of macrophages and PMN's, in addition to leading to augmented cytotoxicity and phagocytosis, causes a variety of biochemical and other changes in these cells. Among the products of activated macrophages and PMN's are a variety of enzymes, which can be expressed on the cell surface or released from the cells and which may be involved in the mechanisms of cytotoxicity (*32*). In addition, macrophages have been shown to produce a series of immunoregulating products, including lymphocyte activating

Table 1. General characteristics of NK cells and other effector cells.

| Morphology | T cells | Monocytes or macrophages | Polymorphonuclear leukocytes | NK cells |
|---|---|---|---|---|
| Size | Small (9 to 12 μm in diameter) | Large (16 to 20 μm) | Large (12 to 18 μm) | Medium (12 to 15 μm) |
| Ratio of cytoplasm to nucleus | Low | High | High | High |
| Nucleus | Round | Markedly indented | Multilobed | Slightly indented |
| General features | | | | |
| Adherence to surfaces | − | + | + | − |
| Phagocytosis | − | + | + | − |
| Cell surface markers | | | | |
| Receptors for sheep erythrocytes (human cells) | Have high-affinity receptors | − | − | + on about 50 percent; have low-affinity receptors |
| Receptors for IgG | Less than 10 percent of cells have receptors | + | + | + |
| Antigens | | | | |
| Human | Most or all cells react with 9.6, OKT3; subsets react with OKT4, OKT8 | Most or all cells react with OKM1, anti-asialo GM1; subsets react with anti-Ia | Most or all cells react with OKM1, anti-asialo GM1 | Most or all cells react with OKM1, anti-asialo GM1, OKT10; subsets react with 9.6 anti-Ia |
| Mouse | All cells express Thy 1, Lyt 1 | Most or all cells express Mac 1, asialo GM1, Mph1 | | Most or all cells express asialo GM1, NK 1, NK 2, Ly11, Ly5, Qa5, ? Mph1 |

factor, which has activating effects on T cells (*33*); interferon (*34*); prostaglandins, particularly of the E series (PGE) (*35*); and colony-stimulating factor (CSF). The production of interferon, PGE, and CSF is of particular interest since each of these molecules can appreciably affect the growth or functions of macrophages themselves as well as of other cell types.

In contrast to T cells, the interaction of macrophages or PMN's with target cells does not depend on well-defined antigenic specificities. They can kill a wide range of syngeneic, allogeneic, and xenogeneic target cells, but some selectivity for certain targets, mainly malignant cells, has been demonstrated (*25, 36*). There is no evidence for a clonal distribution of cells reacting with particular target cells or for a need to recognize products of the major histocompatibility complex on the targets.

## Morphological Characteristics of Natural Killer Cells

Natural killer cells are nonadherent and nonphagocytic cells that have been found in most normal individuals of a wide range of mammalian and avian species (*4*). They express surface receptors for the Fc portion of IgG and most thereby appear to also function as the K cells that mediate antibody-dependent cytotoxicity against tumor target cells (*37*). Although NK cells clearly are not thymic-dependent, with high levels of activity being detectable in athymic nude or neonatally thymectomized mice and rats (*4, 38*), they have been found to share a variety of T cell–associated markers. About half of human NK cells express receptors for sheep erythrocytes (*39*) and the majority react (*23*) with some monoclonal antibodies (9.6, and 3A1) to T cell–associated antigens (*6, 40*). Similarly, at least half of mouse NK cells were shown to express Thy 1 (*41*) and about 20 percent reacted with a monoclonal antibody to Lyt1 (*42*). Also, the monoclonal antibody OX8, directed against a subpopulation of rat T cells with suppressor activity, reacts with a large proportion of rat NK cells (*43*). NK cells also grow in response to TCGF (*44, 45*) and produce TCGF (*46*). Furthermore, a highly enriched population of human NK cells proliferates in response to T cell mitogens, phytohemagglutinin, and concanavalin A (*45*). In contrast to such evidence for a relation between NK cells and T cells, NK cells also share some cell surface markers with macrophages and PMN's. In the human, each of these cell types reacts with OKM1 and antibodies to asialo GM1 and Mac 1 (*47*), and in the mouse, one group of investigators has detected a macrophage-associated antigen, Mph 1, on a considerable proportion of NK cells (*48*).

Particularly because of the conflicting evidence as to the relation of NK cells to well-known categories of lymphoid cells, much effort has been directed toward the identification of markers restricted to, or at least highly selective for, NK cells. The best such marker to date has been a morphologic one: recent evidence indicates that virtually all human and rat NK activity is mediated by large granular lymphocytes (LGL) (*49*), which comprise only about 5 percent of the peripheral blood or splenic leukocytes in man and other species. LGL can be readily identified in Giemsa-stained lymphoid cells prepared on slides in a cytocentrifuge, and they can be highly enriched by centrifugation on density gradients of Percoll (*49, 50*). It now appears that LGL account for a high proportion of human $T_G$ cells (*51*), whose relation to typical T cells has also recently been questioned (*52*). A monoclonal antibody OKT10 reacts with most human LGL but not with other peripheral blood leukocytes (*23*). However, this antigen is not entirely specific for LGL, since it is also expressed on most thymocytes and a subpopulation of bone marrow cells (*53*). Several surface antigens are also expressed, with some selectivity, on most or all mouse NK cells (*54*). However, none of these markers is restricted only to NK cells. Further, in contrast to LGL, which account for virtually all of the natural cytotoxic reactivity against a wide range of target cells (*55*), most of the alloantigenic markers on mouse NK cells have not been found on the related natural cytotoxic (NC) effector cells that react with some solid tumor target cells (*56*).

## Functional Characteristics of Natural Killer Cells

Natural killer cells share a number of features with macrophages and PMN's. As with these other effector cells, NK cells have spontaneous activity in normal individuals and their activity can be rapidly augmented, particularly by interferon (*57*) but also by other stimuli (*58, 59*). However, like T cells, and in contrast to macrophages and PMN's, NK cells can proliferate in response to TCGF. As with all of the other types of effector cells, the activity of NK cells appears to be well regulated, subject to a variety of inhibitory cells and factors (*59*).

The nature of target cell recognition by NK cells seems to be intermediate between the exquisite specificity of T cells and the ill-defined or absent specificity of macrophages or PMN's (*60*). NK cells can react against a wide variety of syngeneic, allogeneic, and xenogeneic cells. Susceptibility to cytotoxic activity is not restricted to malignant cells; fetal cells, virus-infected cells, and some subpopulations of thymus cells, bone marrow cells, and macrophages are also sensitive to lysis. It appears that NK cells can recognize at least several, widely distributed antigenic specificities, and that such recognition is clonally distributed (*60*). Despite this analogy with antigen recognition by T cells, recognition by NK cells does not seem to require expression of products of the major histocompatibility complex on target cells and there is no evidence for a memory response by NK cells. However, some similarity to a memory response has been seen with NK cells, since exposure to NK-susceptible cell lines in vivo or in vitro can rapidly activate NK cells, via induction of interferon (*61*).

The nature of this recognition for interferon production and for cytotoxic interactions of NK cells with target cells is not clear. Some investigators have suggested that NK cells have T cell–like receptors (*62*), whereas others have postulated lectin-like receptors (*63*). The mechanisms of killing by NK cells are also unclear, but, as with T cells, binding to target cells is first required, followed by the lytic event (*64*). The actual lysis may be mediated by neutral serine proteases, by phospholipases, or by both, since inhibitors of these enzymes can block cytotoxicity by NK cells (*64*). Such enzymes or other cytotoxins may be released from NK cells during the cytotoxic interaction (*65*). In contrast to macrophages or PMN's, for which myeloperoxidase appears to play a major role in their cytotoxic effects, such generation of reactive oxygen species is not likely to be involved in lysis by NK cells. Recently, patients with myeloperoxidase deficiency have been found to have normal levels of NK activity (*66*). Furthermore, it has not been possible to detect production of reactive oxygen species by purified populations of human LGL (*64*).

Similar to each of the other effector cell types, NK cells have direct cytotoxic effects against target cells and also can produce and release soluble factors. Best

documented is the ability of NK cells to produce interferon (*61, 67*). In recent studies with highly enriched populations of human LGL, various tumor cell lines, viruses, mitogens, and bacterial and other adjuvants were shown to induce considerable production of interferon after culture overnight (*61*). Of particular note was that during these short-term incubations, only the LGL and not T cells or monocytes produced interferon in response to most of the stimuli. Human LGL, upon incubation with concanavalin A plus phorbol ester, also produced low amounts of TCGF (*46*). These observations are of interest from at least three standpoints. First, they indicate that NK cells may be able to serve as important immunoregulatory cells, providing accessory function for a variety of immune responses that are affected by interferon or TCGF. Second, it appears that NK cells may be able to react with foreign materials in a multifaceted way, by producing soluble factors that can induce antiviral resistance and cytostasis of tumor cells, as well as by direct cytotoxic effects. Third, the ability of NK cells to rapidly produce interferon and possibly TCGF provides a mechanism for positive self-regulation.

## Function of NK Cells Against Tumors in vivo

Until recently, much attention was focused on a central role of T cells in immune surveillance, particularly against cancer. However, it has become increasingly clear that T cell–mediated immunity alone cannot account for resistance against development of tumors or against infection by various microbial agents. For example, athymic nude or neonatally thymectomized mice do not have particularly high incidences of various types of spontaneous or carcinogen-induced tumors, and are quite resistant, at least during the initial phases of infection, to growth of some microbial agents (*68*). These exceptions to a central role for T cells have led to much general skepticism and pessimism as to whether there is any type of immunological protection against cancer [for example, see (*69*)]. However, rather than rejecting the basic hypothesis of immune surveillance (*70*), it seems more realistic to consider the possible involvement of other effector cells, including NK cells. In view of the nature of the processes required for development of T cell–mediated immunity, it is not surprising that they alone would not be sufficient for protection against disease. As already discussed, there is a requisite lag period between exposure to foreign materials, be they cancer cells or microbes, and development of specific immunity. Also, some invaders have poorly expressed or even absent antigenic structures that can trigger T cell immunity.

It seems reasonable, therefore, to postulate a primary, broader-range defense system that can respond almost immediately to foreign materials and at least partially control them, until the more potent and specific immune system begins to respond adequately. The natural cellular immune system, consisting of NK cells, macrophages, and PMN's, seems to be well-suited to play important roles in the postulated primary line of defense. It is not possible, and perhaps not even reasonable, to try to decide which of the various effector cells is most important. Each may have an appreciable role and their relative contributions may vary with different types of tumors or microbial agents and with the particular situation. Also, the various effector cells can interact with each other in a complex variety of ways and thereby influence each other's activities.

Table 2. Some functional characteristics of NK cells and other effector cells.

| Functional characteristics | T cells | Monocytes or macrophages | Polymorphonuclear leukocytes | NK cells |
|---|---|---|---|---|
| Spontaneous reactivity | − | + | + | + |
| Period for development or augmentation of cytotoxic reactivity | Primary response, > 5 to 7 days; memory response, 2 to 5 days | In vivo, 5 to 10 days; in vitro, 18 hours for most stimuli | In vitro, within minutes | In vivo, within 4 hours; in vitro, within 1 hour |
| Nature of target | Wide array of specific antigens and important role of major histocompatibility complex | Specificity not clearly defined; selectivity for tumor targets | Apparently nonspecific but some selectivity for tumor targets | At least several, widely distributed antigenic specificities |
| Cytotoxic reactivity against IgG antibody-coated targets | − | + | + | + |
| Activating factors | Specific antigens, lectins, lymphocyte activating factor (LAF), T cell growth factor (TCGF), interferon, T cell helper factors | Macrophage activating factor, interferon, wide variety of foreign materials (for example, bacterial endotoxin, phorbol esters) | Contact, lectins, cytochalasin E, phorbol esters | Interferon, lectins, antibodies, retinoic acid, TCGF, prostaglandin E (PGE) |
| Inhibition of reactivity | Specific and nonspecific T suppressor cells and factors, macrophage suppressor cells, interferon, PGE, cyclic AMP | PGE, phorbol esters | Inhibitors of serine esterases | PGE, nonspecific macrophage and other suppressor cells, phorbol esters, cyclic AMP |
| Factors promoting their growth | TCGF | CSF | CSF | TCGF |
| Possible mechanisms of cytotoxic effects | Protease, osmotic | Reactive oxygen species, protease, lysozyme, phagocytosis, PGE, interferon | Reactive oxygen species, protease, lysozyme, phagocytosis | Protease, lipase, cytotoxin |
| Production of soluble mediators | Wide array of lymphokines | LAF, colony stimulating factor (CSF), PGE, many enzymes, interferon | Many enzymes | Interferon, possibly TCGF |

Most of the evidence for a role of NK cells in vivo relates to resistance against the growth of NK-susceptible tumor cell lines in vivo. The major approach has been to look for correlations between resistance in vivo to the growth of implanted tumor cell lines and the levels of NK activity in the recipient animals. In a variety of situations, tumors have grown less well in recipients with high NK activity than in those with low activity (*71*). Furthermore, it has been possible to transfer increased resistance against tumor growth, and increased clearance of intravenously or subcutaneously inoculated radioactively labeled tumor cells, by transfer of NK cell–enriched populations or of bone marrow precursors of NK cells (*72*).

Although such results are encouraging, they do not indicate whether NK cells also can have a similar role in defense against growth and metastasis of spontaneous or carcinogen-induced primary tumors. Much less evidence for this issue is available. However, it has been found that most spontaneous mammary tumors of C3H mice (*73*) and spontaneous lymphomas in AKR mice (*74*) have detectable, albeit low, susceptibility to lysis by NK cells. Similarly, some human leukemias, a myeloma, and some carcinomas, sarcomas, and melanomas (*75–78*) have been significantly lysed by NK cells. Such lysis has been appreciably augmented, and thereby evident with a higher proportion of tumors, when the effector cells were pretreated with interferon (*76–78*). As further support for the ability of NK cells to recognize primary tumor cells, Ortaldo *et al.* (*79*) showed that a variety of human tumor cells could inhibit the lysis of radioactively labeled K562 cells.

Most of these positive results were obtained with NK cells from normal allogeneic donors. In fact Vanky *et al.* (*77*) detected NK reactivity only against allogeneic human tumor cells and concluded that the NK cells of the tumor-bearing individual lacked the ability to recognize the autologous tumor cells. They postulated that recognition of foreign histocompatibility antigens was involved in lysis by NK cells, particularly those stimulated by interferon. If correct, their hypothesis would virtually preclude a role for NK cells in resistance against primary tumor growth. However, such restriction of NK reactivity to allogeneic tumors does not fit the many examples of tumor cell lines being susceptible to syngeneic NK cells [see, for example (*80, 81*)]. Similarly, normal C3H mice are reactive against some syngeneic mammary tumors (*73*), and some cancer patients also have had detectable, interferon-augmentable, NK activity against their autologous tumor cells (*78*).

The reasons for the discrepancies among the human studies are not clear. The positive results were obtained with ovarian carcinoma cells, mainly in 20-hour cytotoxicity assays (*78*), whereas the allo-restricted results involved other types of tumors, tested only in 4-hour assays. The greater sensitivity of the prolonged assay would seem sufficient to account for the differences. In addition, it is possible that the subpopulation of NK cells that is required to interact with certain types of tumors may be selectively inhibited in the autologous tumor-bearing host.

Another line of evidence indicating that NK cells may interact in vivo with autologous primary tumor cells is the demonstration that NK cells can enter and accumulate at the site of tumor growth. NK cells have been detected in small spontaneous mouse mammary carcinomas (*82*) and in small primary mouse tumors induced by murine sarcoma virus (*82, 83*). In contrast, NK activity has usually been undetectable in large tumors in mice (*82*) or in clinical specimens of tumors. This may be due, at least in part, to the presence of suppressor cells, which have been demonstrated in some cell suspensions from some tumors (*82, 84*).

Several pieces of evidence suggest that NK cells may be involved in surveillance against primary tumors. One of the major predictions of the immune surveillance theory is that tumor development should be associated with, and in fact be preceded by, depressed immunity. Several observations fit this prediction: (i) Patients with the Chediak-Higashi syndrome, who have a selective and marked deficit in NK activity (*85*), have a high incidence of lymphoproliferative diseases (*86*). (ii) Similarly, in a colony of beige mice with an analogous selective deficit in NK activity (*87*), a high incidence of lymphomas was noted (*88*). (iii) Kidney allograft recipients who have received immunosuppressive drugs and have a high risk of developing lymphoproliferative and other tumors also have severely depressed NK activity (*89*).

A related prediction of the immune surveillance theory is that carcinogenic agents cause depressed immune function, thereby impairing the ability of the host to reject the transformed cells. This postulate has been examined by many investigators in regard to the possible role of mature T cells and humoral immunity, and conflicting results have been obtained (*90*). In contrast, the initial and still fragmentary data on this point in relation to NK cells are promising: (i) Urethane, which produces lung tumors in only some strains of mice, caused transient and marked depression of NK activity in a susceptible strain but not in resistant strains (*91*). Administration of normal bone marrow, which can reconstitute NK activity, to urethane-treated susceptible mice reduced the subsequent development of lung tumors (*92, 93*). (ii) Multiple, low doses of irradiation of C57BL mice, which is highly effective in inducing leukemia in this strain, produced a substantial deficit in NK activity (*94*). The depressed NK activity could be restored by transfer of normal bone marrow cells from C57BL mice but not from beige mice (*93*), and such transfer of normal C57BL bone marrow has been reported to interfere with radiation-induced leukemogenesis (*95*). (iii) Carcinogenic doses of dimethylbenzanthracene in vivo (*96*), and treatment of lymphoid cells in vitro with two different classes of tumor promoters, phorbol esters and teleocidin (*64*), have produced inhibition of NK activity. Each of these observations supports the possibility that one of the requisites for tumor induction by carcinogenic agents may be interference with host defenses, including those mediated by NK cells.

### Other Functions of NK Cells in vivo

There is also increasing evidence for a role of NK cells in resistance against some microbial infections. Most of the studies have related to virus infections in animals, with several investigators showing that resistance to infection by some viruses is correlated with NK activity. Lopez (*97*) has accumulated considerable evidence for a role of NK cells in genetic resistance of mice to severe infection by herpes simplex type I. It also seems likely that NK cells play an important role in natural resistance to infection by mouse cytomegalovirus (*98*). There are also some indications that natural genetic resistance to another herpes virus, Marek's disease virus in chickens, may be mediated by NK cells (*99*). However, there is also evidence against a role for NK cells in resistance to some other viruses (*100*).

Natural killer cells may also be involved in resistance against some other types of microbial infections. Recently, a correlation was found between levels of NK activity and resistance of mice to the protozoan parasite *Babesia microti* (*101*). A possible role for NK cells has also been found for natural resistance of

mice to infection by the fungus *Cryptococcus neoformans* (*102*).

In line with the evidence that NK cells can react against some normal cells, there is increasing evidence for a major role of NK cells in natural resistance against bone marrow transplants. For many years it has been recognized that mice have natural resistance to transplantation of normal bone marrow and that some of the characteristics of this phenomenon do not conform to the well-established rules governing transplantation of other tissues. With the development of information about the characteristics of NK cells, it has become clear that NK cells might account for this resistance to bone marrow transplants. Indeed, in a series of direct comparisons between the characteristics of natural resistance to bone marrow transplants and of NK cells, an excellent correlation was found and it is now generally agreed that NK cells are the main effector cells for this phenomenon in vivo (*103*). It is of interest that a relation has also been observed between NK cell activity and graft versus host disease (*104, 105*).

## Conclusions and Prospects

Natural killer cells represent an interesting and unusual type of effector cell. Research to date has led to a considerable level of understanding of the nature and characteristics of these cells, but has also raised a number of questions. For example, it would be of interest to determine more clearly the lineage of NK cells and their relation to the T cell and myelomonocytic lineages; the nature of the recognition receptors on NK cells and of the antigens on the target cells; the detailed mechanisms for the regulation of their activity; and the biochemical sequence of events that lead to their lysis of target cells. The recent finding of the intimate association between NK cells and LGL, and the concomitant ability to purify these cells and to expand their numbers in culture, have provided an excellent basis for further studies on these questions. It would also be of interest to determine the nature of the granules in LGL and whether these granules play an important role in their functions.

The data on the roles of NK cells in vivo suggest that these cells may be important in the first line of defense against tumor growth and against infection by some microbial agents. It is now necessary to determine more directly the role of NK cells in immune surveillance. Ideally, one would like to show increased tumorigenesis when NK activity is selectively depressed and reduced tumor formation when such deficiencies are selectively reconstituted or normal levels of reactivity are selectively augmented. However, there are several practical problems in conducting such experiments. In addition to the long time needed for such studies and difficulties in identifying the most relevant experimental carcinogenesis models, completely selective and sustained alterations of NK activity are not easily found or produced. Furthermore, the NK-depressive effects of carcinogens themselves might eliminate the differences between normal and NK-deficient individuals. The most convincing procedure might be to reconstitute animals with depressed NK activity, by adoptive transfer of purified NK cells or their precursors, and determine the effects on carcinogenesis or on microbial infections. If a major role for NK cells in resistance against tumor growth or other diseases can be substantiated, this might lead to alternative strategies for immunoprevention or immunotherapy.

The findings of a major role for NK cells in natural resistance against bone marrow transplants in mice have considerable implication for clinical bone marrow transplantation. If NK cells can be shown to be similarly involved in rejection of human bone marrow transplants, some alterations in current procedures might be made to ensure sustained depression of NK activity, which might thereby improve graft survival.

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